General

Guideline Title

Guidelines for the identification and management of substance use and substance use disorders in pregnancy.

Bibliographic Source(s)

World Health Organization (WHO). Guidelines for the identification and management of substance use and substance use disorders in pregnancy. Geneva (Switzerland): World Health Organization (WHO); 2014. 204 p. [93 references]

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Regulatory Alert

FDA Warning/Regulatory Alert

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- August 31, 2016 – Opioid pain and cough medicines combined with benzodiazepines : A U.S. Food and Drug Administration (FDA) review has found that the growing combined used of opioid medicines with benzodiazepines or other drugs that depress the central nervous system (CNS) has resulted in serious side effects, including slowed or difficult breathing and deaths. FDA is adding Boxed Warnings to the drug labeling of prescription opioid pain and prescription opioid cough medicines and benzodiazepines.
- March 22, 2016 – Opioid pain medicines : The U.S. Food and Drug Administration (FDA) is warning about several safety issues with the entire class of opioid pain medicines. These safety risks are potentially harmful interactions with numerous other medications, problems with the adrenal glands, and decreased sex hormone levels. They are requiring changes to the labels of all opioid drugs to warn about these risks.

Recommendations

Major Recommendations

The definitions for the strength of the recommendations (strong, conditional) and the quality of evidence (high, moderate, low, very low) are provided at the end of the "Major Recommendations" field.

Recommendation 1

Health-care providers should ask all pregnant women about their use of alcohol and other substances (past and present) as early as possible in the pregnancy and at every antenatal visit. (Strength of recommendation: Strong; Quality of evidence: Low)

Remarks

- Asking at every visit is important as some women are more likely to report sensitive information only after a trusting relationship has been solidly established.
- Pregnant women should be advised of the potential health risks to themselves and to their babies posed by alcohol and drug use.
- Validated screening instruments for alcohol and other substance use and use disorders are available (see Annex 3 in the original guideline document).
- Health-care providers should be prepared to intervene or refer all pregnant women who are identified as using alcohol and/or drugs (past and present).
- It was decided that despite the low quality of evidence of effect, the benefit – potential reduction of alcohol and substance use – outweighed any potential harms of a brief psychosocial intervention, which were considered minimal. Therefore the balance of benefits versus harms was clearly positive despite uncertainty about the degree of benefit. In addition, the burden of implementation was minimal.

Recommendation 2

Health-care providers should offer a brief intervention to all pregnant women using alcohol or drugs. (Strength of recommendation: Strong; Quality of evidence: Low)

Remarks

- Brief intervention is a structured therapy of short duration (typically 5–30 minutes) offered with the aim of assisting an individual to cease or reduce the use of a psychoactive substance. It is designed in particular for general practitioners and other primary health-care workers.
- Health-care providers should be given appropriate training and resource materials.
- The brief intervention should be individualized, and include feedback and advice on ceasing or reducing alcohol and other substance use during pregnancy. There may need to be follow-up with the patient, with the possibility of referral to treatment for those patients who are unable to reduce or eliminate such use.
- The approach/attitude of health-care providers is an important contributor to the effectiveness of brief interventions.
- As for Recommendation 1, it was decided that, despite the low quality of evidence of effectiveness, this should be a strong recommendation because the potential benefit – reduction of alcohol and/other substance use – likely outweighs any potential harms of a brief psychosocial intervention which were considered minimal. Therefore the balance of benefits versus harms was clearly positive, although there was uncertainty about the degree of benefit. In addition the burden of implementation was minimal.

Recommendation 3

Health-care providers managing pregnant or postpartum women with alcohol or other substance use disorders should offer comprehensive assessment and individualized care. (Strength of recommendation: Conditional; Quality of evidence: Very low)

Remarks

- A comprehensive assessment of women using alcohol or drugs in pregnancy and the postpartum period includes an assessment of patterns of substance use, medical or psychiatric comorbidity, family context, as well as social problems.
- Individualized care involves selecting appropriate psychosocial interventions of different intensity based on the particular needs of the pregnant women and the resources available. Psychosocial interventions include a number of psychological treatments and social supports, ranging from lesser to higher intensity. The psychosocial treatment and support referred to in this section is a more intensive set of interventions typically delivered by people with specific training in the management of substance use disorders, and usually includes repeated contact with the patient. The kinds of specific psychological techniques considered in this category include cognitive behavioural therapy, contingency management and motivational interviewing/enhancement. The kinds of social support referred to in this section include assistance with accommodation, vocational training, parenting training, life-skills training, legal advice, home-visiting and outreach.
- Despite the benefits of psychosocial treatment outweighing the harms, this recommendation was considered to be conditional given the absence of strong evidence and the potential resource implications.

Recommendation 4

Health-care providers should, at the earliest opportunity, advise pregnant women dependent on alcohol or drugs to cease their alcohol or drug use

and offer, or refer to, detoxification services under medical supervision where necessary and applicable. (Strength of recommendation: Strong; Quality of evidence: Very low)

Remarks

- Pregnant women dependent on alcohol or drugs who agree to undergo detoxification should be offered the supported withdrawal from substance use in an inpatient or hospital facility, if medically indicated.
- Detoxification can be undertaken at any stage in pregnancy, but at no stage should antagonists (such as naloxone, or naltrexone – in the case of opioid withdrawal) be used to accelerate the detoxification process.
- Equal attention should be paid to the health of mother and fetus during detoxification and treatment adjusted accordingly.
- The exceptions to this recommendation are opioid and benzodiazepine dependence, which are covered by Recommendations 5 and 6 separately.
- It was decided that this recommendation should be strong, despite the very low quality of evidence of the effectiveness of the health-care intervention because there is clear evidence of harm to the fetus of ongoing maternal substance use, and the benefit to both mother and fetus of ceasing alcohol and/or substance use under medical supervision strongly outweighs any potential harms.

Recommendation 5

Pregnant women dependent on opioids should be encouraged to use opioid maintenance treatment whenever available rather than to attempt opioid detoxification. (Strength of recommendation: Strong; Quality of evidence: Very low)

Remarks

- Opioid maintenance treatment in this context refers to either methadone maintenance treatment or buprenorphine maintenance treatment.
- Pregnant patients with opioid dependence who wish to undergo detoxification should be advised that relapse to opioid use is more likely following medication-assisted withdrawal than while undertaking opioid maintenance treatment.
- Such medication-assisted withdrawal from opioids should be attempted only in an inpatient unit, using a gradual reduction in methadone or buprenorphine doses. Inpatient care should also be considered for the initiation and optimization of maintenance treatment.
- Psychosocial treatment should be an integral component of such treatment.
- Pregnant women who fail to complete medication-assisted withdrawal should be offered opioid agonist pharmacotherapy.
- It was decided that this recommendation should be strong despite the low quality of evidence of effectiveness from randomized controlled trials, as the rate of relapse to opioid use following detoxification has been shown to be high and the risks of harm to both mother and fetus from failed detoxification are catastrophic compared to the very low risks of harm from opioid maintenance treatment.

Recommendation 6

Pregnant women with benzodiazepine dependence should undergo a gradual dose reduction, using long-acting benzodiazepines. (Strength of recommendation: Strong; Quality of evidence: Very low)

Remarks

- Long-acting benzodiazepines should only be used for as short a time as is medically feasible in managing benzodiazepine withdrawal.
- Psychosocial interventions should be offered throughout the period of benzodiazepine withdrawal.
- Inpatient care should be considered in the withdrawal management of pregnant women with benzodiazepine dependence.
- It was decided that this recommendation should be strong despite the very low quality of evidence of effectiveness because ongoing benzodiazepine use in pregnancy is associated with significant risk of harm. At the same time, abrupt cessation of benzodiazepines can result in a severe withdrawal syndrome including seizures and psychosis. This leaves gradual reduction as the only practicable alternative. Significant clinical experience indicates that this approach is feasible and safe. Hence the Guideline Development Group (GDG) was in agreement that the benefits of gradual dose reduction outweigh the harms of both ongoing use and abrupt cessation.

Recommendation 7

Pregnant women who develop withdrawal symptoms following the cessation of alcohol consumption should be managed with the short-term use of a long-acting benzodiazepine. (Strength of recommendation: Strong; Quality of evidence: Very low)

Remarks

- Management of alcohol withdrawal usually also includes administration of thiamine.
- Alcohol withdrawal management may be facilitated by the use of an alcohol-withdrawal scale such as the Clinical Institute Withdrawal

Assessment for Alcohol-revised (CIWA-Ar).

- Inpatient care should be considered in the withdrawal management of pregnant women with alcohol dependence.
- Alcohol withdrawal can be a severe and even life-threatening condition, provoking seizures and delirium. Evidence from non-pregnant populations has demonstrated the effectiveness of long-acting benzodiazepines for preventing seizures and delirium in alcohol withdrawal. Given the severity of alcohol withdrawal, and the lack of significant harm from short-term benzodiazepine use, and the evidence supporting the use of benzodiazepines in the management of alcohol withdrawal in the general population, the GDG decided that this recommendation should be strong despite the low quality of evidence in pregnant women.

Recommendation 8

In withdrawal management for pregnant women with stimulant dependence, psychopharmacological medications may be useful to assist with symptoms of psychiatric disorders but are not routinely required. (Strength of recommendation: Strong; Quality of evidence: Very low)

Remarks

- Except for the management of acute intoxication, withdrawal management in amphetamine-type stimulants (ATS) dependence or cocaine dependence does not include psychopharmacological medications as a primary approach to treatment in pregnant patients. There is no evidence that medication-assisted withdrawal would benefit pregnant women with these respective disorders.
- Inpatient care should be considered in the withdrawal management of pregnant women with stimulant dependence.
- It was decided that this recommendation should be strong despite the very low quality of evidence because the harms to mother and fetus of ongoing use of psychostimulants have been shown to be high. The risks of providing short-term appropriate non-teratogenic medications for short-term management of psychologically distressing symptoms in pregnancy are very low. Therefore, the potential benefits of this approach strongly outweigh the harms of providing psychopharmacological treatment of symptoms, if required, during psychostimulant withdrawal.

Recommendation 9

Pharmacotherapy is not recommended for routine treatment of dependence on amphetamine-type stimulants, cannabis, cocaine or volatile agents in pregnant patients. (Strength of recommendation: Conditional; Quality of evidence: Very low)

Remarks

- For pregnant patients who use cannabis, amphetamine-type stimulants, cocaine, and volatile agents, the focus of treatment should be on psychosocial interventions.
- The recommendation was considered conditional given the complete lack of research on this issue.

Recommendation 10

Given that the safety and efficacy of medications for the treatment of alcohol dependence has not been established in pregnancy, an individual risk benefit analysis should be conducted for each woman. (Strength of recommendation: Conditional; Quality of evidence: Very low)

Remarks

- Pregnant patients with alcohol dependence should be offered psychosocial interventions.
- The recommendation was considered conditional given the complete lack of research on this issue.

Recommendation 11

Pregnant patients with opioid dependence should be advised to continue or commence opioid maintenance therapy with either methadone or buprenorphine. (Strength of recommendation: Strong; Quality of evidence: Very low)

Remarks

- Pregnant patients with opioid dependence should be encouraged to commence opioid agonist pharmacotherapy, which should be combined with psychosocial interventions.
- Opioid-dependent pregnant women who are already taking opioid maintenance therapy with methadone should not be advised to switch to buprenorphine due to the risk of opioid withdrawal. Pregnant opioid-dependent women taking buprenorphine should not be advised to switch to methadone unless they are not responding well to their current treatment.
- In opioid-dependent pregnant women, the buprenorphine mono formulation should be used in preference to the buprenorphine/naloxone formulation.

- Regardless of the choice of medication, psychosocial interventions should be an integral component of treatment.
- Opioid-dependent pregnant patients who wish to receive opioid antagonist pharmacotherapy should be discouraged from such a choice.
- It was decided that this recommendation should be strong despite the low quality of evidence as the rate of relapse to opioid use following detoxification is high and the risks of harm from failed detoxification are catastrophic compared to the small risks of harm from opioid maintenance treatment.

Recommendation 12

A. Mothers with substance use disorders should be encouraged to breastfeed unless the risks clearly outweigh the benefits.
B. Breastfeeding women using alcohol or drugs should be advised and supported to cease alcohol or drug use; however, substance use is not necessarily a contraindication to breastfeeding. (Strength of recommendation: Conditional; Quality of evidence: Low)

Remarks

- A risk assessment should take into account the risks of exposure to alcohol and drugs in breast milk, human immunodeficiency virus (HIV) status, the specific pattern of substance use in each case, the availability of safe and affordable breast milk substitutes, as well as access to clean water, sterilizing equipment, and the age of the infant/child. Heavy daily alcohol consumption, such as in alcohol dependence, would constitute high risk to the infant, for example, and in the presence of safe breast milk alternatives, it would be preferable not to breastfeed.
- The message to breastfeeding women who have used alcohol and drugs to cease using alcohol and drugs while breastfeeding should be given in such a way that it does not undermine the potential benefits of breastfeeding.
- It is possible to reduce the risk of exposure through breastfeeding by altering the timing of breastfeeding, or by the use of temporary alternatives, such as stored (frozen) breast milk or breast milk substitutes where they are available and can be safely used. Women who use alcohol intermittently should be discouraged from breastfeeding for 2 hours after consuming one standard drink (10 g of pure alcohol), and 4 to 8 hours after consuming more than one drink in a single occasion. Breastfeeding advice for women with HIV should also take into consideration the risk of HIV transmission (refer to the WHO guidelines on breastfeeding and HIV).
- Mothers of infants with a neonatal withdrawal syndrome should be offered appropriate breastfeeding information and support.
- This recommendation was considered conditional because the different values and preferences of women and the lack of strong evidence of harms of low levels of substance use in pregnancy.

Recommendation 13

Skin-to-skin contact is important regardless of feeding choice and needs to be actively encouraged for a mother with a substance use disorder who is able to respond to her baby's needs. (Strength of recommendation: Strong; Quality of evidence: Low)

Remarks

- It was decided that the recommendation should be strong despite the very low quality evidence as the risk of harm is minimal, it consumes no resources, the values and preferences were in favour of the recommendation, and there was considered to be certainty about the balance between benefits and harms.

Recommendation 14

Mothers who are stable on opioid maintenance treatment with either methadone or buprenorphine should be encouraged to breastfeed unless the risks clearly outweigh the benefits. (Strength of recommendation: Strong; Quality of evidence: Low)

Remarks

- Women prescribed opioids such as methadone and buprenorphine and wishing to stop breastfeeding may wean their children off breast milk gradually to reduce the risk of developing withdrawal symptoms.
- It was decided that the recommendation should be strong, as, despite the low quality of evidence of effect, it was considered highly likely that the benefit of avoiding withdrawal symptoms in the infant strongly outweighed any potential harms. The values and preferences expressed by end-users surveyed were strongly in favour of the recommendation and there was certainty about the balance between benefits and resources being consumed.

Recommendation 15

Health-care facilities providing obstetric care should have a protocol in place for identifying, assessing, monitoring and intervening, using non-pharmacological and pharmacological methods, for neonates prenatally exposed to opioids. (Strength of recommendation: Strong; Quality of evidence: Low)

Remarks

- Evidence of a dose-response relationship between opioid maintenance treatment and neonatal withdrawal syndrome has been inconsistent, which implies that all infants should be assessed.
- Infants exposed to opioids during pregnancy should remain in the hospital at least 4 to 7 days following birth and be monitored for neonatal withdrawal symptoms using a validated assessment instrument, which should be first administered 2 hours after birth and then every 4 hours thereafter.
- Non-pharmacological interventions including low lights, quiet environments, swaddling and skin-to-skin contact should be used with all neonates prenatally exposed to alcohol and drugs.
- It was decided that the recommendation should be strong despite the low quality of evidence of effect, as the GDG agreed that the benefits of such an approach strongly outweighed any potential harms. The values and preferences of end-users were in favour of the recommendation, and there was certainty that while resources would be consumed, the benefits strongly outweighed costs. There was a high value placed on identifying preventable suffering in affected neonates.

Recommendation 16

An opioid should be used as initial treatment for an infant with neonatal opioid withdrawal syndrome if required. (Strength of recommendation: Strong; Quality of evidence: Very low)

Remarks

- Prolonged treatment of neonatal opioid withdrawal syndrome with opioids is generally not necessary and aiming for shorter treatment is preferable.
- Phenobarbital can be considered as an additional therapy if there has been concurrent use of other drugs in pregnancy, particularly benzodiazepines, and if symptoms of neonatal opioid withdrawal are not adequately suppressed by an opioid alone. If opioids are unavailable, phenobarbital can be used as an alternative therapy.
- Infants with signs of a neonatal withdrawal syndrome in the absence of known maternal opioid use should be fully assessed for possible benzodiazepine, sedative or alcohol exposure.
- The strong recommendation to use opioids rather than phenobarbital despite the very low quality of evidence of effectiveness was based on vast clinical experience with opioids in the management of both adult and neonatal opioid withdrawal. There has only been very limited clinical experience with phenobarbital use. In addition, the values and preferences of end-users were in favour of the recommendation, and the GDG agreed that there was certainty about the balance between benefits and resources being consumed.

Recommendation 17

If an infant has signs of a neonatal withdrawal syndrome due to withdrawal from sedatives or alcohol or the substance the infant was exposed to is unknown, then phenobarbital may be a preferable initial treatment option. (Strength of recommendation: Conditional; Quality of evidence: Very low)

Remarks

- Infants with signs of a neonatal withdrawal syndrome in the absence of known maternal opioid use should be fully assessed for possible benzodiazepine, sedative, or alcohol exposure.
- This recommendation was considered conditional because of the lack of high-quality evidence and the lack of certainty of the balance between benefits and harms.

Recommendation 18

All infants born to women with alcohol use disorders should be assessed for signs of fetal alcohol syndrome (FAS). (Strength of recommendation: Conditional; Quality of evidence: Very low)

Remarks

- Signs of FAS include growth impairment, dysmorphic facial features (short palpebral fissures, smooth or flattened philtrum, thin upper lip) and central nervous system abnormalities, including microcephaly.
- When assessing such infants the following information should be recorded:
    - Birthweight and length
    - Head circumference
    - Dysmorphic facial features

    - Gestation
    - Prenatal exposure to alcohol
    - Follow-up of infants with signs of FAS should be provided
- This recommendation was considered conditional because of the lack of high-quality evidence, and questions about the feasibility of implementation in all settings.

Definitions:

Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group Grades of Evidence

High quality: Further research is very unlikely to change confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.

Very low quality: The Guideline Development Group is very uncertain about the estimate.

Strength of Recommendation

- Strong: The Guideline Development Group (GDG) was confident that the quality of the evidence of effect, combined with certainty about the values, preferences, benefits and feasibility, made this a recommendation that should be done in most circumstances and settings.
- Conditional: There was less certainty about the quality of the evidence and values, preferences, benefits and feasibility of this recommendation. Thus, there may be circumstances or settings in which it should not apply.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Substance use and substance use disorders in pregnancy

Guideline Category

Counseling

Evaluation

Management

Prevention

Risk Assessment

Screening

Treatment

Clinical Specialty

Family Practice

Nursing

Obstetrics and Gynecology

Pediatrics

Preventive Medicine

Intended Users

Advanced Practice Nurses

Health Care Providers

Nurses

Physician Assistants

Physicians

Psychologists/Non-physician Behavioral Health Clinicians

Public Health Departments

Social Workers

Substance Use Disorders Treatment Providers

Guideline Objective(s)

- To provide evidence-based technical advice to health-care providers on identifying and managing substance use and substance use disorders in pregnant women, which enables health-care practitioners to apply the scientific principles of a public health approach in their own countries
- To enable pregnant women to make healthy decisions about alcohol and other substance use in the context of pregnancy and breastfeeding

Target Population

- Pregnant or postpartum women using alcohol, illicit drugs, or other psychoactive substances
- Infants exposed to alcohol and other psychoactive substances

Interventions and Practices Considered

1. Screening and brief interventions for hazardous and harmful substance use during pregnancy
2. Comprehensive assessment and individualized care
3. Psychosocial intervention for substance use disorders in pregnancy
4. Detoxification or quitting programs for substance dependence in pregnancy, including management of withdrawal symptoms
5. Pharmacological treatment (maintenance and relapse prevention) for substance dependence in pregnancy
6. Breastfeeding
7. Management of infants exposed to alcohol or other psychoactive substances

Major Outcomes Considered

Maternal

- Substance use
- Withdrawal/withdrawal severity
- Retention in substance use treatment

- Identification of substance use
- Provision of intervention for substance use
- Referral to relevant treatment of substance use
- Ongoing substance use during pregnancy
- Bonding with child
- Well-being
- Mastitis
- Termination of maternal rights (e.g., baby taken into care)

Fetal/Neonatal

- Opioid withdrawal
- Intrauterine growth retardation
- Birth defects
- Neonatal abstinence syndrome
- Gestational age at delivery
- Birthweight
- Spontaneous abortion
- Head circumference at birth
- Neonatal death
- Weight gain/days to regain birthweight
- Attachment
- Failure to thrive
- Neurobehaviour (lethargy, sedation, irritability)
- Infections
- Feeding issues
- Treatment failure
- Seizures
- Total length of hospital stay
- Duration of withdrawal treatment

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Searches of Unpublished Data

Description of Methods Used to Collect/Select the Evidence

Criteria for Considering Studies for This Review

Types of Studies

1. Randomized controlled trials (RCTs)
2. Systematic reviews and/or meta-analyses categorized as:
    - Cochrane reviews from any year
    - Non-Cochrane systematic review conducted between 2008 and 2013
    - Non-Cochrane systematic reviews conducted prior to 2008

The Guideline Development Group (GDG) determined *a priori* that systematic reviews conducted prior to 2008 would require extensive updating and therefore chose to focus on evaluating Cochrane reviews regardless of year and non-Cochrane reviews published since 2008.

Types of participants and interventions varied by evidence question.

Search Methods for Identification of Studies

The search was conducted by using a search strategy developed in consultation with the World Health Organization (WHO) Pregnancy and Substance Use Guidelines Technical Team. The search was iterative and the strategy was refined to ensure that it had maximum sensitivity to identify all relevant RCTs.

Electronic Searches

The search strategy was developed with the assistance of the WHO Information Specialist. A comprehensive and exhaustive search strategy was formulated in an attempt to identify all relevant RCTs, systematic reviews and meta-analyses regardless of language or publication status (published, unpublished, in press, and in progress).

The RCT strategy developed by The Cochrane Collaboration and detailed in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) was combined with the PubMed strategy for systematic reviews together with database-specific terms for pregnancy, lactation and the postpartum period. This was combined with database-specific terms for substance use, abuse and dependence. The search was not limited to specific substances or interventions as the search was intentionally general to be applicable to all evidence questions to be addressed during the guideline process.

The search was iterative and a number of trial searches were run first to ensure maximal sensitivity.

The following databases were searched (see search strategies in Annex 2 in the original guideline document):

- Medline via PubMed - search conduced on 9 June 2013
- EMBASE - search conducted on 10 June 2013
- PsycINFO - search conducted on 10 June 2013
- CINAHL - search conducted on 10 June 2013
- Cochrane Central Register of Controlled Trials (CENTRAL) - search conducted on 13 June 2013

Searching Other Resources

The GDG checked the reference lists of all studies identified by the above methods and examined any systematic reviews, meta-analyses, or guidelines identified during the search process for references.

The GDG was in close contact with individual researchers working in the field, and policymakers based in intergovernmental organizations including WHO and United Nations Office on Drugs and Crime (UNODC).

Data Collection and Analysis

Selection of Studies

Two of the review authors inspected all citations from the electronic search and identified relevant abstracts of trials and systematic reviews for inclusion criteria. The full text articles were obtained for all potentially relevant studies and one of the authors assessed each of these for eligibility. This process was duplicated by the other author and two interns.

Where there were uncertainties or disagreements, or where disputes could not be resolved, these studies remained in awaiting assessment or ongoing studies and the authors were contacted for clarification. The two review authors made final decisions regarding inclusion.

Number of Source Documents

After electronic and manual deduplication using ENDNOTE software, 5632 records were screened, of which 172 were identified as potentially eligible randomized controlled trials (RCTs) and 73 systematic reviews and the full texts for these were obtained. A total of 93 articles were deemed eligible for inclusion. See Table 2 in the original guideline document for a breakdown of the number of articles and distinct RCTs by evidence retrieval area.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group Grades of Evidence

High quality: Further research is very unlikely to change confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.

Very low quality: The Guideline Development Group is very uncertain about the estimate.

Methods Used to Analyze the Evidence

Meta-Analysis of Randomized Controlled Trials

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Data Collection and Analysis

Data Extraction and Management

Data Extraction

One guideline author extracted data from included studies. A second author checked each data entry. The disputes were resolved by discussion. If it was not possible to extract data or if further information was needed, attempts were made to contact the study authors. The extracted data was presented only in tables and figures whenever possible, and when further information was necessary, the study authors were contacted in order to obtain missing data or for clarification of methods.

Management

Forms

Data was extracted onto standardized, simple forms, including:

- Administrative details: Trial or study identification number; author(s); published or unpublished; year of publication; number of studies included in paper; year in which study was conducted; details of other relevant papers cited
- Details of the study: Study design; type, duration and completeness of follow-up; country and location of study (e.g., higher-income vs. lower-income country); informed consent and ethics approval
- Details of participants: Setting, numbers, relevant baseline characteristics including age
- Details of intervention: Type of intervention, timing and duration of intervention, additional co-interventions
- Details of comparison: Type and comparison, timing and duration of comparative intervention
- Details of outcomes: Maternal and infant outcomes
- Details of the analysis: For randomized controlled trials (RCTs), details of the type of analysis (intention-to-treat or per protocol)

Scale-derived Data

Continuous data from rating scales were included only if:

- The psychometric properties of the measuring instrument have been described in a peer-reviewed journal.

- The measuring instrument has not been written or modified by one of the trialists for that particular trial.

Ideally the measuring instrument should either be i) a self-report or ii) completed by an independent rater or relative (not the therapist). This is not often reported clearly and this was noted to assist in the risk of bias assessment.

Endpoint Versus Change Data

There are advantages of both endpoint and change data. Change data can remove a component of between-person variability from the analysis. On the other hand, calculation of change needs two assessments (baseline and endpoint), which can be difficult in unstable and difficult to measure conditions such as substance dependence. The Guideline Development Group (GDG) decided to primarily use endpoint data, and only use change data if the former were not available. The GDG combined endpoint and change data in the analysis rather than standardized mean differences throughout.

Skewed Data

Continuous data on clinical and social outcomes are often not normally distributed. To avoid the pitfall of applying parametric tests to non-parametric data, the GDG aimed to apply the following standards to all data before inclusion:

- Standard deviations and means are reported in the paper or obtainable from the authors.
- When a scale starts from the finite number zero, the standard deviation, when multiplied by two, is less than the mean (as otherwise the mean is unlikely to be an appropriate measure of the centre of the distribution.

Endpoint scores on scales often have a finite start and end point and these rules can be applied. The GDG entered skewed endpoint data from studies of fewer than 200 participants as other data within data and analyses rather than into a statistical analysis. Skewed data pose less of a problem when looking at means if the sample size is large; such endpoint data was entered into syntheses.

When continuous data are presented on a scale that includes a possibility of negative values (such as change data), it is difficult to tell whether data are skewed or not. For these cases, skewed change data were entered into analyses regardless of size of study.

Common Measure

To facilitate comparison between trials, the GDG intended to convert variables that can be reported in different metrics, such as days in hospital (mean days per year, per week or per month) to a common metric (e.g., mean days per month).

Direction of Graphs

Where possible, data were entered in such a way that the area to the left of the line of no effect indicated a favourable outcome for the treatment intervention. Where keeping to this made it impossible to avoid outcome titles with clumsy double-negatives (e.g., 'Not improved'), the GDG reported data where the left of the line indicates an unfavourable outcome. This was noted in the relevant graphs (see the original guideline document).

Assessment of Risk of Bias in Included Studies

One review author worked independently by using criteria described in the *Cochrane Handbook for Systematic Reviews of Interventions* to assess trial quality. This set of criteria is based on evidence of associations between overestimate of effect and high risk of bias of the article such as sequence generation, allocation concealment, blinding, incomplete outcome data and selective reporting.

Please see Annex 2 in the original guideline document for information on the systematic review methodology for the following:

- Measures of treatment effect
- Unit of analysis issues
- Dealing with missing data
- Assessment of heterogeneity
- Assessment of reporting biases

Data Synthesis

Where RCTs were found to be methodologically or clinically comparable, the GDG pooled trial results in a meta-analysis. Where the presence of statistical heterogeneity was found, the data were combined using the random effects model.

For meta-analysis of RCTs, the GDG combined the results and the relative risk and the 95% confidence intervals for dichotomous data. For

continuous data, the GDG combined the mean differences to calculate a weighted mean difference and standard deviation.

Subgroup Analysis and Investigation of Heterogeneity

Heterogeneity was explored by conducting sub-group analyses between:

1. Type of substance dependence
2. Setting of treatment (e.g., inpatient versus outpatient)

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Individuals and Partners Involved in Development of the Guidelines

World Health Organization (WHO) Steering Group

An internal steering group was drawn from the WHO departments of Mental Health and Substance Abuse, Reproductive Health and Research, Gender Equity and Human Rights, and the Tobacco Free Initiative. The full list of names is provided in Annex 4 of the original guideline document.

Guideline Development Group

The Guideline Development Group (GDG) was made up of people with content expertise, relevant experience in health care in low- and middle-income countries and expertise in evidence-based guideline methodology. The GDG selection also ensured gender balance and regional diversity. Members have been drawn from all WHO regions.

Consultants with expertise in evidence search and Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology supported the GDG. The full list of the GDG members and consultants along with their expertise, affiliations and geographical base is provided in Annex 4 in the original guideline document.

External Review Group

External reviewers were drawn from end-users, agencies and partners working in the subject area of the guidelines. Their names, affiliations, areas of interest and geographical base are given in Annex 4 in the original guideline document.

External reviewers were asked to evaluate and comment at different stages of development of the guidelines. Some members of the external review group attended the initial scoping meeting and the final recommendation decision meeting as 'special invitees' where they acted as observers providing comments but had no involvement in decision-making. They reviewed the scoping questions, outcomes of interest, evidence profiles, and the final guideline document. Reviewer response was compiled and comments used to refine the scope of the guidelines, the outcomes of interest, and the final recommendations.

How the Guidelines Were Developed

The development of these guidelines began in mid 2012 as a collaborative effort between the WHO departments of Mental Health and Substance Abuse and the Tobacco Free Initiative with production of the guidelines proposal, a virtual meeting of the GDG, and subsequent approval of the guidelines proposal by the WHO Guidelines Review Committee. The GDG has conferred through teleconferences and virtual meetings, as well as at two face-to-face meetings. At the first meeting, held in Washington DC, USA (29 January to 1 February 2013), the evidence for the harms of different patterns of alcohol and drug use in pregnancy was reviewed, and the scope and areas of evidence retrieval were established. At the second and final meeting, held at the WHO Headquarters in Geneva (11–13 September 2013) the evidence retrieved was presented using evidence profiles and GRADE tables (see Annex 1 in the original guideline document), and final recommendations were formulated.

A values and preferences survey was conducted over three weeks in August 2013. Respondents – many of them health-care workers or pregnant (or recently pregnant) women – were asked to rate their preference for each draft recommendation and to provide comments on how it might affect them. At the final face-to-face guideline development group meeting, held in September 2013, an analysis of the responses was presented during discussion of each recommendation. These results were used by the GDG to weigh values and preferences when setting the strength of each recommendation. The form can be accessed at: https://sryyz.enketo.formhub.org/webform .

Evidence to Recommendations

The GRADE system for assessing quality of evidence and using evidence to inform decisions was applied by the GDG when drafting the final recommendations. For each of the six areas of scoping focus, an evidence profile was provided summarizing the evidence retrieved, including evidence on values, preferences, benefits, harms and feasibility. Wherever possible, the evidence retrieved was evaluated using GRADE and GRADE tables were provided. Evidence of effectiveness was rated as high, moderate, low or very low depending on the certainty of effect measured in the studies evaluated. For many of the EVIDENCE questions the evidence was either lacking or very limited, leading to a rating of very low quality evidence. The GDG recognized that extensive research needs to be done to provide a solid evidence base for management of pregnant women with substance use and substance use disorders. A decision table was used by the GDG to assess and agree on the quality of evidence and certainty about harms and benefits, values and preferences, feasibility and resource implications (see Annex 1 in the original guideline document for details of each decision, presented in Evidence Profiles 1–6).

Decisions were usually made by consensus but where there was disagreement, the GDG members voted and a two-thirds majority was required for a decision to be carried. Where a two-thirds majority was not achieved initially, it was agreed that the recommendation should be reworded and a vote taken again. This was necessary in only one instance – for recommendation 8, concerning management of stimulant withdrawal.

Rating Scheme for the Strength of the Recommendations

Strength of Recommendations

- Strong: The Guideline Development Group (GDG) was confident that the quality of the evidence of effect, combined with *certainty* about the values, preferences, benefits and feasibility, made this a recommendation that should be done in most circumstances and settings.
- Conditional: There was less certainty about the quality of the evidence and values, preferences, benefits and feasibility of this recommendation. Thus, there may be circumstances or settings in which it should not apply.

Cost Analysis

Refer to Annex 1 in the original guideline document for information on costs and resource use.

Method of Guideline Validation

External Peer Review

Description of Method of Guideline Validation

External reviewers were asked to evaluate and comment at different stages of development of the guidelines. Some members of the external review group attended the initial scoping meeting and the final recommendation decision meeting as 'special invitees' where they acted as observers providing comments but had no involvement in decision-making. They reviewed the scoping questions, outcomes of interest, evidence profiles, and the final guideline document. Reviewer response was compiled and comments used to refine the scope of the guidelines, the outcomes of interest, and the final recommendations.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Potential Benefits

Appropriate identification and management of substance use and substance use disorders in pregnancy to help achieve healthy maternal, fetal, and neonatal outcomes

See Annex 1 in the original guideline document for benefits of specific interventions.

Potential Harms

Screening and Brief Interventions

- Unpleasant symptoms associated with reduction or cessation of alcohol or substance use
- Potential legal or social consequences for disclosing use
- Social consequences – problematic interaction with partners/peers associated with reduction or cessation of alcohol or substance use
- Cessation may interfere with activities of daily living.
- Referral for cessation intervention may induce time and economic burdens.

Interventions for Harmful Use and Dependence on Alcohol and Other Substances in Pregnancy

- Psychosocial physical and mental symptoms associated with reduction or cessation of alcohol or substance use
- Possible development of depression or anxiety as a result of cessation or reduction of alcohol or illicit substance use
- Possible verbal and/or physical abuse by the partner as a result of the pregnant woman's behaviour change
- Possible risk of switching from one substance to another substance
- Between 7% and 15% of individuals participating in psychosocial interventions to treat substance use disorders may be worse off after treatment than before treatment. This decline in functioning may be due to a lack of bonding with the provider, lack of goal direction and monitoring, confrontation, criticism, and high emotional arousal and stigma.
- Stigmatization-risk of incarceration/loss of infant in punitive systems
- Economic and time burdens imposed by need to attend interventions
- Conflict with partner/family/employer over time/commitment to intervention

Detoxification or Quitting Programmes for Alcohol and Other Substance Dependence in Pregnancy

- The success of medication-assisted withdrawal during pregnancy is generally considered to be poor, with estimates of failure as low as 41% and as high as 96%. Failure rate is difficult to estimate precisely, because some authors have defined failure as failure to complete detoxification, while others have defined failure as return to substance use. This failure is associated with a number of negative outcomes, including increased fetal exposure to illicit substances and other maternal risk behaviours, reduced compliance with obstetrical care, and poorer neonatal birth parameters.
- High risk of relapse to opioids following opioid detoxification
- High risk of relapse to benzodiazepines following detoxification
- Often stressful short-term symptoms associated with reduction or cessation of alcohol or substance use
- Little development of coping skills
- Increased risk of fetal stress (depending on the substance)
- Increased risk of fetal morbidity or mortality, including miscarriage and stillbirth
- Possible development of depression or anxiety as a result of cessation or reduction of alcohol or illicit substance use
- Possible risk of switching from one substance to another substance
- Damage to relationships/loss of employment

Pharmacological Treatment (Maintenance and Relapse Prevention) for Alcohol and Other Substance Dependence in Pregnancy

- Unpleasant side effects due to the pharmacological intervention or uncovered withdrawal from alcohol or substance use
- Possible development of depression or anxiety as a result of cessation or reduction of alcohol or illicit substance use
- Methadone and buprenorphine both reduce additional opioid use in pregnancy, but the neonate often develops a withdrawal syndrome referred to as neonatal abstinence syndrome (NAS)
- Possible risk of drug substitution
- Increased risk of fetotoxicity
- Possible increased risk of congenital defects and anomalies related to exposure to the pharmacological intervention (particularly for acamprosate, naltrexone, nalmefene, disulfiram, benzodiazepines)

Breastfeeding

- Potential higher risk of difficulties bonding due to neonatal withdrawal symptoms
- Short- and long-term risks of the child being exposed via breast milk to varying amounts of substances consumed by the mother. These risks depend on the substance consumed by the mother, with little data available for several substances (e.g., hallucinogens, volatile agents). The most harmful exposures are alcohol (>50 gms in one occasion).
- Risk that a mother who is using sedative substances may inadvertently suffocate the child
- Greater risk exposure of breastfed child to chaotic lifestyle harms such as violence, maternal drug seeking/prostitution
- Maternal psychopathology may enhance risk to breast fed child.

Management of Infants Exposed to Alcohol and Other Psychoactive Substances

- Risk of adverse neonatal response to pharmacological agent. Buprenorphine may have less adverse impact than methadone on fetal neurobehaviour.
- There may be a higher incidence of non-serious maternal adverse events, particularly non-serious maternal cardiovascular events, associated with methadone than buprenorphine. No differences were found in between the two medications for neonatal adverse events.
- Early identification of fetal alcohol syndrome (FAS) may stigmatize children and their mothers.

Qualifying Statements

Qualifying Statements

- The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of the World Health Organization (WHO) concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.
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Implementation of the Guideline

Description of Implementation Strategy

Plans for Disseminating, Adapting, and Implementing These Recommendations

These recommendations will be used to provide guidance on the identification and management of substance use and substance use disorders in pregnancy through a range of derivative publications including training materials and a manual describing how best to put these recommendations into practice. This will be widely disseminated through the World Health Organization (WHO) regional and country offices, collaborating centres, professional organizations and partner agencies.

Local Adaptation/Implementation of These Recommendations

These recommendations will be adapted for the field by developing suitable training materials in consultation with regional, national and local stakeholders. Adaptation will include translation into appropriate languages and ensuring that the interventions are acceptable in local sociocultural contexts suitable for local health systems.

Refer to the original guideline document for suggested methods for measuring the impact of these recommendations.

Implementation Tools

Audit Criteria/Indicators

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Staying Healthy

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

World Health Organization (WHO). Guidelines for the identification and management of substance use and substance use disorders in pregnancy. Geneva (Switzerland): World Health Organization (WHO); 2014. 204 p. [93 references]

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2014

Guideline Developer(s)

World Health Organization - International Agency

Source(s) of Funding

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Guideline Committee

World Health Organization (WHO) Steering Group

Guideline Development Group (GDG)

Composition of Group That Authored the Guideline

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Financial Disclosures/Conflicts of Interest

All Guideline Development Group members, external reviewers and consultants completed the World Health Organization (WHO) declaration of interest forms. Several Guideline Development Group (GDG) members declared academic and financial interests. These were then reviewed by the secretariat for potential conflicts of interest (see summary in Annex 5 in the original guideline document). Hendree Jones had received funding from Reckitt Benckiser, a manufacturer of buprenorphine. She received small honoraria for presenting at conferences, and received free buprenorphine for use in her clinical trials. Gabriele Fischer received a small amount of consultancy funding from Reckitt Benckiser, a manufacturer of buprenorphine, Mundipharma, a manufacturer of morphine, and Lannacher, a manufacturer of psychiatric medication. Anju Dhawan had received funding for a clinical trial from Rusan Pharmaceuticals, a manufacturer of both methadone and buprenorphine. As these members are well-recognized researchers and clinicians in this field and, taking into consideration the level of funding, it was agreed that they should not be excluded from the GDG but that these potential competing interests should be managed by excluding them from active discussion and decision-making related to the pharmaceuticals produced by companies from which they had received funds. Both meetings began with an open declaration of interests. It was made clear that those GDG members with pharmaceutical industry funding could not participate in discussions on questions related to the medications associated with such companies.

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Electronic copies: Available from the World Health Organization (WHO) Web site .

Print copies: Available from the WHO Press, World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland; Phone: +41 22 791 3264; Fax: +41 22 791 4857; E-mail: bookorders@who.int.

Availability of Companion Documents

The following is available:

- WHO handbook for guideline development. Geneva (Switzerland): World Health Organization (WHO); 2012. 56 p. Electronic copies: Available from the World Health Organization (WHO) Web site .

In addition, suggested methods for measuring the impact of these recommendations are available in the original guideline document .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on February 24, 2015. This summary was updated by ECRI Institute on June 2, 2016 following the U.S. Food and Drug Administration advisory on opioid pain medicines. This summary was updated by ECRI Institute on October 21, 2016 following the U.S. Food and Drug Administration advisory on opioid pain and cough medicines combined with benzodiazepines.

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